DISCUSSION OF PAPER BY FRANCES PASCHER, M.D.: SYSTEMIC REACTIONS TO TROPICALLY APPLIED DRUGS*

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IT would be presumptuous of me to speak authoritatively to this audience on any facet of dermatology. As an internist, however, I should like to tell you of a fairly common complication of the external application of adrenal steroid ointments.

Dr. Frances Pascher has already alluded at length to some facets of this problem. Let us explore another. Perhaps a case history will illustrate what I have in mind.

The patient was a 47-year-old white woman who developed dermatitis venenata. The skin lesions were vesicular and they drained. To them an occlusive adrenal steroid ointment was applied. The patient was extremely uncomfortable and she applied the ointment liberally because of her distress. After 19 days of this application she began to note some lassitude and somnolence. Her bowel habits, which had normally required no attention, became poor. Her abdomen became distended. Her heart rate became rapid, and it was this symptom, associated with shortness of breath, which brought her to the hospital. I had the opportunity to see her at this point with her physician.

On examination she answered questions listlessly and often erroneously. Her heart rate was 180 per minute and regular. There were no murmurs. Her abdomen was grossly distended. She was so weak that she was unable to sit up by herself in bed nor could she stand. The muscles of her arms and legs seemed like a half-filled water bottle, so

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that if one pressed on one end of the extremity there was typical ballottement on the other.

There were rales in both lungs. The appearance of this cardiac difficulty associated with obvious congestive heart failure was surprising to her physician because she had never exhibited any evidence of heart disease. Her physician had digitalized her prior to my visit and at about this time she became anuric. Her admitting diagnosis was auricular flutter with congestive heart failure and anuria probably based on a low cardiac output because of the marked tachycardia. Her electrolyte studies at admission showed serum sodium of 129, potassium of 5, bicarbonate of 38, and chloride of 84. These are not numbers with which dermatologists must contend frequently, but suffice it to say that the potassium and sodium were normal, the bicarbonate quite high, and the chloride lower than normal.

The patient was suffering from potassium depletion. You will notice that I have avoided calling this hypokalemia, and the reason for this is that in potassium-depleted states the blood-potassium levels bear no relation to the state of the intracellular-potassium level. Potassium, as you are well aware, is the largest single cation within the cells, there being 155 mEq. intracellularly, whereas sodium measures only 14. In the serum these numbers are almost directly reversed, for the normal sodium in the serum is 145, whereas normal potassium is about 5. This patient had a normal serum potassium because she was pouring potassium out of her cells. This increased the level within the transport mechanism, the serum—the only place where this ion can be conveniently measured. But while the levels within her cells were constantly dropping enough to produce paralytic ileus—the somnolence, her cardiac failure, and the anuria with which she presented the blood levels remained normal. These findings are all consistent with intracellular potassium deficiency in each of these target organs. All these were initiated by the use of large doses of steroids. The important point to make here is that steroids were not administered by injection nor were they taken by mouth. They were applied to the skin and were absorbed by the skin in sufficient quantity to produce this almost disastrous result.

This patient's rapid heart rate was due to paroxysmal auricular tachycardia with block, a condition which appears almost completely in potassium depletion. Upon the administration of potassium this block disappeared and she resumed a normal sinus rhythm. A renal biopsy

taken on this anuric woman showed the presence of vacuolization in all of the renal tubular cells, a condition that bears the long and complicated name kaleopenicnephropathy, and appears again only in the presence of marked potassium depletion.

Obviously if all cells are losing potassium so do those of the renal tubules, which are unable to function in the absence of a normal potassium level.

Perhaps a word or two of physiology is in order here so that this case and its complications will become crystal clear. Potassium is usually taken in somewhere in the neighborhood of 40 to 70 mEq. per day and the same amount is excreted. Blood levels remain fairly constant and the intracellular levels are equally constant. The mistake of measuring blood-potassium levels in the serum is a common error to which I have already alluded. Serum examinations measure only that small part of potassium that is in transport, about $\frac{1}{27}$th of the total. It is as though one were taking a straw vote to determine who might be elected governor of New York, in which we took a sample of a small number of individuals and then made the mistake of taking the sample in California. Clinically, when we measure potassium in the blood we are measuring only a small proportion of it and we are not measuring it in the cells where it really counts.

When an individual becomes ill it is not unusual for the patient to stop eating. Thus the intake of potassium falls off. This was indeed the case with this patient. When we investigated further after she recovered she admitted that she stopped eating and took only sips of tea because she was so uncomfortable. Her face was swollen as well. The consequence of this then was that she was taking very little potassium and continually excreting 60 to 70 mEq. Over the period of her illness this would represent a loss of 600 to 1,000 mEq. of potassium, a sizable amount—a dangerous amount. To compound the felony, as our legal colleagues are wont to say, we must add to this several other factors which worsened the condition considerably. The stress of this unpleasant, irritating illness was sufficient obviously to stimulate her general adaptation syndrome—a reaction which Dr. Hans Selye of Montreal has emphasized. Stress stimulates the adrenal cortex and this, in turn, causes the outpouring of considerable amounts of adrenal-cortical materials. These substances tend to increase the excretion of potassium by the kidney exchanging it for sodium. Now she had an added intrinsic

source of steroids added to that which she had absorbed through the skin. Thus she now had two sources of steroids even though she was given no corticoids by mouth.

But the problem did not stop even there. You will remember that this patient showed some evidence of congestive heart failure. When this happened the cardiac output naturally falls because the heart is beating ineffectively, the heart muscle is damaged by the lack of potassium just as much as the skeletal muscle. You will recall that on admission to the hospital this woman was practically paralyzed and her intestinal musculature was paralyzed. You will remember the distended abdomen with no peristalsis; thus it is not surprising that her heart was not functioning very well either. The rales in her chest, as well as the arrythmia, either or both, might have proved lethal.

When the cardiac output falls the amount of blood reaching the kidney is reduced. There is a mechanism in the kidney which functions quite well to remedy a falling blood volume. In the juxtoglomerular apparatus, in the afferent branches of the renal artery, are cells which answer only to stretch. When they are not stretched they produce renin which, in turn, activates angiotensin I, a decapeptide. Enzymatic action turns this into angiotensin II by taking off two peptides and leaving an octopeptide. This material is an intense stimulator of the adrenal cortex, causing marked production of aldosterone. It is also our most potent hypertensive material. When aldosterone reaches the distal convulated tubules of the kidney the sodium is resorbed from the tubules and exchanged for potassium, which is then excreted. These two effects normally are an excellent mechanism because the retained sodium attracts water to it, which increases the blood volume, and the patient recovers. However, here we had a patient who was already losing too much potassium and her body, in its efforts to correct the falling blood volume, merely made the potassium losses greater. Our patient then had marked excretion of potassium with little intake and, as a result, she became very deficient in this all-important cation.

Diagnosis

This is a difficult diagnosis to make. One cannot make it by taking blood levels of potassium. When they are low it is very helpful. But the levels are usually normal and may even be high because the individual is pouring potassium out of his cells. Blood-potassium levels are

relatively useless. One laboratory feature that is frequently helpful—it was in this case—is that potassium is excreted in combination with some anion, usually chloride, so that the blood chloride is frequently low. In order to maintain the proper *p*H of the body the ubiquitous bicarbonate appears, and this was higher than normal from a normal of 27 to 38. This is one of the few laboratory leads. The electrocardiogram does become abnormal in potassium depletion but, unfortunately, this cannot be depended upon in every instance to make the diagnosis for us because many of these patients will have abnormal cardiograms from prior heart disease, and the superimposition of the potassium depletion on top of the previous problem will make for an obscure change which may not be readily diagnosed. We get back therefore to clinical acumen. It must be suspected in any patient whose food intake is falling off, who is under stress, who is receiving adrenal steroids—by any route—in anyone with diarrhea or vomiting, who is receiving nasogastric suction, or who is receiving parenteral fluids that do not contain potassium.

On examination the muscles are flabby; they feel, as I indicated earlier, like a half-filled water bottle. The body lies in almost a cadaverous manner on the table without any rounding but flattening out against the bed. The abdomen is distended, there are cardiac symptoms, there are renal symptoms—as this patient had—and there are central nervous symptoms of serious disease. Of all of these factors the most important is to suspect it because it is not a dramatic, easily made diagnosis.

Treatment

Obviously the treatment is to replace the loss of potassium. The amount of potassium administered is as much as the body can take, and one discovers this by taking a blood potassium before beginning treatment and watching it at hourly intervals as potassium is infused to determine whether or not it is rising precipitously. If the blood levels rise the potassium is not getting into the cells and the rate of administration must be slowed. Too much potassium is as bad as too little; both are fatal. As soon as possible, potassium in the form of chloride should be given by mouth and there are several palatable means of doing this. Do not expect that the patient's diet will handle this problem for you. It would require 15 to 18 oranges a day to supply at least 100 mEq. of potassium or perhaps 20 to 24 bananas, so that one must depend upon exogenous potassium chloride in large quantities. Potassium in pill

form should not be used as it is likely to produce ulcerations and even stenosis and perforation of the intestines. It must be a liquid. Realize that your patient is in a deficit of at least 1,000 mEq. of potassium. He is going to lose 70 mEq. of what you give him every day, so that even if you give him 100 mEq. of potassium he will save only 30 of these. It will probably be necessary to treat him for a month. Do not think that because the patient has received a few sips of potassium-containing solution or been infused with 40 mEq. in his intravenous you have solved this problem. This is about as specious a bit of reasoning as to think that one can water an acre of lawn with a medicine dropper.

Of most importance is not the treatment of this disease but rather its prevention because, for the most part, it is iatrogenic. We produce it, and we ought to be able to prevent it, so that if a patient becomes anorexic or is under stress or is receiving steroids or is vomiting or having diarrhea, then get potassium into this individual before he gets into as serious a condition as the patient here described. The use of intravenous potassium is perfectly safe as long as the individual is voiding regularly at least 2 cc. per minute. In this instance it was particularly hazardous because our patient was anuric due to her kaleopenicnephropathy. This is the only indication there is for intravenous potassium in the face of anuria. Even then it must be watched carefully to make sure that one does not jump out of the frying pan of potassium depletion into the fire of hyperkalemia, which is equally fatal.

I am especially grateful to have had this opportunity to meet with the Section on Dermatology. I knew Dr. Howard Fox during my internship. It has been a privilege to appear on a program in his honor with Dr. Pascher, a dermatologist of similar stature.